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EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 11/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/627,583	DOSHI, RAJIV	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13,16 and 24-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13,16 and 24-32* is/are rejected.

7)☒ Claim(s) *24 and 25* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-11, 13, 16, 24-32 are pending.
Claims 1-11, 13 and 16 all recite a new combination of claim limitations through amendment of claim 1 and dependence therefrom.
Claims 24-32 are newly submitted claims.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. All prior rejections and objections are herein withdrawn in light of Applicant's claim amendments and cancellation of claims.

Response to Arguments

2. Applicant's arguments with respect to claim1-11, 13, 16 and 24-32 have been considered but are moot in view of the new ground(s) of rejection.

Claim Objections

3. Claims 24-25 are objected to because of the following informalities:

4. Claims 24 and 25 recite the phrase "with delivery device"; a transitional article ---a--- is missing. Claim 24 recites the phrase "in manner sufficient"; a transitional article ---a--- is missing. Appropriate correction is required.

Please Note: In light of the definition of "neurotoxin" provided at page 6 paragraph 2, the following prior art rejections are being made of record, wherein the neurotoxin inhibits acetylcholine release from nerve endings or may inhibit release of other neurotransmitters including oxide, glycine, GABA, serotonin, dopamine, epinephrine, and norepinephrine from nerve terminals. Representative neurotoxins listed include botulinum toxin, tetanus toxin, terodotoxin, bungotoxin, terodotoxin, conotoxin and derivatives thereof, etc.

Claim Rejections - 35 USC § 102

5. Claims 1-4, 6,9-11, 13,24-28 are rejected under 35 U.S.C. 102(e) as being anticipated by Cruz et al (US **Pat. 6,630,516).**

Instant claim 1, 24-31: Cruz et al disclose the instantly claimed invention directed to a method that comprises the steps of:

Emptying the bladder of the host (see col. 5, line 12 "urine was emptied")

Intravesically (see col. 2, line 67 "intravesicular instillation") administering into the lumen of the bladder (see col. 5, lines 38-45 ""RTX solution was introduced into an emptied bladder, retained in the bladder for 30 minutes, then the bladder was emptied") of said host an effective (see col. 2, lines 64-67 "based on experimental evidence of effective therapy in humans") amount of a neurotoxin (see col. 1, lines 15-25 "RTX", "TYX", "capsaicin", "desensitizing sensory nerves") together with a neurotoxin permeability modulating agent (See col. 10, lines 24-45 "dimethyl sulfoxide" , "ethanol") to treat said host for said urologic disorder (see col. 3, line 15 "incontinence"),

wherein said administering comprises employing a delivery device with an inflatable component (see col. 5, lines 34-45 "An 18 or 20 F three-way Foley catheter was used. The balloon was inflated to 20 ml and maintained gently pulled against the bladder neck to reduce leakage of RTX") and

said method comprises inflating said inflatable component prior to, during or after administration of said neurotoxin (see col. 5, lines 34-45).

Instant claim 2, 29: wherein said host is human (see col. 2, line 65 "effective therapy of humans").

Instant claims 3-4, 30-31: wherein the urologic disorder is a bladder disorder (see title "urinary incontinence therapy").

Instant claim 6, 9: the method further comprises the intravesically administering at least one neurotoxin permeability-modulating agent (see col. 10, lines 24-56: "in combination with ethanol, and one other" including "dimethyl sulfoxide" and "co-solvents"), wherein the administering is simultaneously

Instant claim 10: further comprises administering to said host at least one additional agent to treat said urologic condition (the additional agent being a permeability agent: see col. 10, lines 24-45; or "a prophylactic antibiotic" (see col. 5, lines 19-21).

Instant claim 11, 25: wherein said delivery device is a catheter (see col. 5, line 34 "Foley catheter was used. The balloon was inflated").

Instant claim 13: wherein said neurotoxin is administered in a reservoir (see col. 11, lines 5-18 "means for transferring the instillation dose to the patient" and "syringes or multi-chambered containers having a breachable internal seal separating active ingredient from diluent").

Cruz anticipates the instantly claimed invention.

6. Claims 24 , 26-27 and 28-32 are rejected under 35 U.S.C. 102(e) as being anticipated by Chancellor et al (US PG-Pub 2003/0108597 A1, filing date August 13, 2002; priority date August 13, 2001).

Chancellor et al disclose the instantly claimed invention directed to a method of treating a host suffering from a urologic disorder, the method comprising the steps of:

Instant claim 24: Intravesically (see [0019, page 3, line 3 "intravesical instillation]) administering into the lumen ("[T]hese antibodies may be conjugated to the surface of the liposome, and act to target the liposome to specific cell types and/or receptors"]) of the bladder (see [0021, page 3, line 3, "disorders of the bladder"]) of said host an effective amount of a neurotoxin (see [0022, page 3, "botulinum toxins"]) to treat [0018, page 3 "improved treatments", ""e.g. IC, hyperactive bladder"; also see Example 6, page 22, [0197]-[0199] the urologic disorder [0021, page 3, "IC, or other conditions of the bladder, such as bladder infection and bladder cancer"],

Instant claims 24 and 27:Wherein the administering is done in a manner sufficient to enhance neurotoxin contact with the inside of the bladder (see page 3, [0021, "In specific embodiments,

these vehicles may comprise vanilloids, e.g. capsaicin, resiniferatoxin or tinyatoxin and may further comprise surface antibodies, e.g. uroplakin or NGF receptor antibodies, to target pain relief to the affected sites.) The antibodies serving to enhance neurotoxin contact through targeting the drug delivery device to cells inside the bladder.

Instant claims 24 and 26: The delivery device (liposomes delivered through a transurethral bladder catheter (see [0150], are disclosed to include antibodies which serve to fix an element (liposomes comprising bladder cell targeted antibodies) within the bladder. see [0019 antibodies on surface of liposome with toxins, to include "botulinum toxin")]).

An additional method disclosed by Chancellor et al includes the steps of:

Instant claim 28:

Emptying the bladder of the host (see [0150 "to elicit repetitive voiding", the term "voiding" being an equivalent term for the phrase: "emptying of the bladder"];

Intravesically administering at least one neurotoxin permeability modulating agent to said host (see [0151, "infusion of protamine sulfate (PS) to increase epithelial permeability", prior to administration of neurotoxin; infusion of KCl during neurotoxin administration (see Figure 1; or infusion of acetic acid after administration (see Figure 1))

Intravesically administer to the lumen of the bladder of said host an effective amount of a neurotoxin (see paragraphs [0139, 0133, 0119, 0111-0112]) to treat said host for said urologic disorder [see Figure 1: Saline→ PS/KCL→ LP/KCL and [0151 "infusion of LP for one hour"]. The meaning of LP is liposomes (see [0147, page 15, col. 2, last paragraph]).

Instant claim 29: wherein the host is human (see page 13, [0105 lines 1-3]).

Instant claim 30: wherein the urologic disorder is a bladder disorder (see page 13, [0103 and 0104, "bladder"]).

Instant claim 31: wherein the bladder disorder is urinary incontinence (see page 13, col. 1, [-1-3, "incontinence".

Instant claim 32: wherein the neurotoxin is botulinum toxin (see page 14, [0111-0112, 0119, 0139, 0133, all claims, especially claims 9-12]).

Chancellor et al anticipates the instantly claimed invention.

Claim Rejections - 35 USC § 103

7. Claims 5, 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cruz et al (US **Pat. 6,630,516)**, as applied to claims 1-4, 6,9-11, 13,24-28 above, in view of Chancellor et al US PG-Pub 2003/0108597 A1.

See discussion of Cruz et al above. Cruz et al describes, teaches and shows a method of treating a host suffering from an urologic disorder through intravesically administering a neurotoxin together with a permeability modulating agent to the lumen of the bladder (infusion to cells of bladder), but differs from the instantly claimed invention by failing to show the neurotoxin to be botulinum toxin, and the permeability modulating agent administered before the intravesically administered neurotoxin.

See discussion of Chancellor above. Chancellor et al describe a method that comprises the step of intravesically administering of botulinum neurotoxin to the lumen of the bladder together with a permeability-modulating agent administered before (see Figure 1) or during

(ethanol, excipient, page 12, [0096]) the botulinum neurotoxin administering step in an analogous art for the purpose of treating a urologic disorder.

It would have been prima fascia obvious the person of ordinary skill in the art at the time the invention was made to modify the neurotoxin of Cruz et al with the botulinum neurotoxin of Chancellor et al because both Cruz et al and Chancellor et al administer a neurotoxin intravesically to a host to treat a urologic disorder and Chancellor et al administers either the toxin of Cruz et al (see Chancellor et al, page 3, [0021] /Cruz et al, see col. 1, lines 15-15) or botulinum toxin (see Chancellor et al, page 3, [0022]) or a combination of both (see Chancellor et al, page 12, [0095-0096] and [0111]) formulated into a delivery vehicle which is non-toxic, reduces irritative side effects and undesirable antigenicity associated with intravesical drug delivery to luminal organ systems (see Chancellor et al, page 3, [0018]).

Additionally Chancellor et al show the administration of a permeability modulating agent prior to, and during the intravesical administration of neurotoxin in an analogous art for the purpose of increasing epithelial permeability and increasing the intercontraction interval (ICI, see page 16, [0148] and Example 2, [0156 "When the infusion fluid was switched to LP/KCL, after a delay of 10-20 minutes, the ICI was significantly increased), wherein an increased intercontraction interval is a desired therapeutic effect when treating urologic disorders associated with incontinence (see Chancellor et al, page 16, [0151 "protamine"], Figure 1] and page 4, [0032]).

Therefore, it also would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to administer the permeability modulating agent prior to the intravesical administration of the neurotoxin because Chancellor et al showed a significant increase in intercontration interval and increased bladder control in hosts suffering from urologic incontinence.

In the absence of a showing of unexpected results, the person of ordinary skill in the art would have been motivated by the reasonable expectation of success of treating a urologic disorder with the botulinum neurotoxin and prior administration of a permeability modulating agent as taught by Chancellor et al in the method of Cruz et al, because both Cruz et al and Chancellor et al successfully treated urologic disorders through the intravesical administration of a neurotoxin to the lumen of the bladder of a host, and Chancellor et al teaches that botulinum neurotoxin may be administered alone or together with the toxin of Cruz et al in a method of treating an urologic disorder and Chancellor et al also found that when a permeability modulating agent has been intravesically administered prior to administration of the neurotoxin, the intercontraction interval between urine emptying events is increased showing the desired therapeutic effect of increased bladder control in patients with urologic incontinence disorders. Cruz et al in view of Chancellor et al obviate the instantly claimed invention.

8. Claims 8 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cruz et al (US **Pat. 6,630,516)**, as applied to claims 1-4, 6,9-11, 13,24-28 above in view of Hildebrand et al (US Pat. 5,861,431, issue date January 19, 1999).

See discussion of Cruz et al above. Cruz et al shows a method of treating a host suffering from an urologic disorder through intravesically administering a neurotoxin inhibitor, the administering step comprising a permeability modulating agent both delivered to the lumen of the bladder (infusion to cells of bladder) with an inflatable component (balloon catheter), but differs from the instantly claimed invention by failing to show the administering step to comprise

the application of an electromotive permeability modulating agent during and after the intravesically administered inhibitor.

Hildebrand et al show a method of treating a host suffering from an urologic disorder comprising the step of intravesically administering an inhibitor to the lumen of the bladder through an inflatable component (see col. 6, lines 31-54, all claims, col. 7, lines 24-27, and claim 6), wherein the administering step comprises an electromotive permeability modulating agent, specifically electromotive drug administration in association with the inflatable component (see Hildebrand et al, col. 6, lines 31-43) in an analogous art for the purpose of driving or dragging the inhibitor through the pores of the inflatable balloon catheter and into the bladder lumen urethral wall, thus enhancing cellular uptake of the inhibitor and (see Hildebrand et al, col. 6, lines 31-39) increased control over urine flow from the bladder (see abstract and all claims).

It would have been prima fascia obvious the person of ordinary skill in the art at the time the invention was made to modify the administering step in the method Cruz et al which includes a permeability modulating agent to also include the electromotive drug permeability modulating agent of Hildebrand et al because Hildebrand et al teaches, provides guidance and shows the electromotive drug permeability modulating agent to be compatible with inflatable balloon catheters, the delivery device used by both Cruz et al and Hildebrand et al in the administering step, wherein the electromotive drug permeability modulating agent served to enhance cellular uptake and attainment of the desired therapeutic effect.

In the absence of a showing of unexpected results, the person of ordinary skill in the art would have been motivated by the reasonable expectation of success of treating a urologic disorder in view of the guidance and teaching of Cruz et al and Hildebrand et al because both

successfully treated urologic disorders through the intravesical administration of an inhibitor to the lumen of the bladder, the delivery device of the inhibitor comprising an inflatable component, and Hildebrand et al provided motivation to apply an electromotive permeability modulating agent for the realized advantage of enhanced cellular uptake and penetration of the administered inhibitor by bladder lumen cells. Cruz et al in view of Hildebrand et al obviate the instantly claimed invention as now claimed.

Conclusion

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US 20040022726A1,US006200257B1,US005437291A , US006802841B2, 5698549, US006464697B1,US006123703A,US006579870B2, US 20030161809A1 are cited to show methods of treating urologic disorders or to disclose the administration of inhibitors nervous system associated molecules.

10. Lewis,Simon A, (2000) is cited to show "Everything you wanted to know about the bladder epithelium but were afraid to ask".

11. This is a non-final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vgp
November 7, 2005

L. F. Smith

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